REMARKS

Claim Rejections Under 35 U.S.C. § 112, First Paragraph

Examiner has rejected claims 1-6, 8, 9 and 22-27 under 35 U.S.C. § 112, First Paragraph as failing to comply with the enablement requirement alleging that the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is mostly nearly connected, to make and/or use the invention. Applicants respectfully traverse this rejection for the reasons given below.

Although the Examiner acknowledges that the claims encompass production of any transgenic ungulate, such as a bovine, having a homozygous deletion of a prion (PRP) gene and using such transgenic ungulate lacking the prion gene and furthermore that the specification indicates that the transgenic ungulates can be used as a source of cells and tissues for xenotransplantation in treating diseases, such as Parkinson's, or Huntington's Disease, or can be used for the production of recombinant proteins in milk. However, the Examiner alleges that the specification fails to provide adequate guidance and evidence for what would be the resulting phenotype of the transgenic ungulate having said homologous deletion of the prion gene or how to use said transgenic ungulates. Applicants respectfully call the Examiner's attention to page 4 lines 16-25 of the specification and the references cited in that paragraph of the specification discussing the phenotype of PrP knockout mice as well as page 17 line 23 to page 18 line 2 which addresses the differences of gene targeting between mice and cattle and the construction of a genomic library to facilitate the gene targeting in cattle.

The Examiner further alleges that the specification fails to provide adequate guidance and evidence for the production and use of a transgenic ungulate or a line of transgenic ungulates bearing that homozygous deletion of the prion gene. Applicants call the Examiner's attention to the incorporation by reference of United States Patent 6,147,276 which, in column 9 lines 35-62, "sets out a typical process by which transgenic and non-transgenic mammals may be prepared." Applicants cite this patent, incorporated by reference, which also addresses optional phenotypic screening, as guidance and the examples immediately following this section as evidence.

Applicants have also amended claims 1 and 22 herein to recite that the resulting phenotype of the transgenic ungulate is one that renders the ungulate less susceptible to prion-

related diseases. Additional support for this amendment can be found throughout the specification, specifically at the following: page 7, lines 16-18, page 8, lines 11-16, page 9, lines 18-30. Applicants reiterate that homozygous deletion of the prion gene would naturally lead to animals wherein the resulting phenotype is one in which the animal is less likely to incur prion-associated diseases. Thus in these animals, prion-associated diseases would occur at a virtually zero rate of incidence in an animal containing such a homozygous deletion.

The Examiner also alleges that the specification fails to provide guidance for how to use said transgenic ungulates. The specification states on page 2, lines 22-25 that "more than one million infected cows may have entered the food chain in the UK" and the specification also cites several pieces of prior art, for example Prusiner S. B. (1997). *Prion diseases and the BSE crisis*. Science 278, 245-251 and Stekel D. J., Nowak M. A. and Southwood T. R. (1996). *Prediction of future BSE spread.* Nature 381, 119. 8. Taylor D. M. (1993), which discuss threat posed by prion infections. Clearly one skilled in the art would easily recognize how to use prion-free ungulates. One skilled in the art would understand that an ungulate lacking the prion gene would provide a superior animal for a variety of different applications and this is discussed throughout the specification, a good example of which is on page 10 line 30 to page 11 line 6. Applicants maintain that such an animal, for example, would be useful for breeding or agricultural purposes as it would not be prone to diseases associated with the prion gene. Therefore these animals and progeny could be useful for meat or milk production for both animals and human consumption.

Additionally such animals could be useful as animal models to study the effect of the prion-gene deletion on phenotype and such animals would have potential applications for the expression of recombinant proteins. Applicants direct the attention of the Examiner to claim 9 that provides for a recombinant bovine to comprises a heterologous gene linked to a mammary-specific promoter. With respect thereto, the use of such a transgenic ungulate for expression of heterologous polypeptides, wherein expression is driven by a mammary-specific promoter is thus well established. In fact, numerous patents have been granted that are directed to the use of transgenic ungulates to produce heterologous polypeptides and their milk because the expression is driven by such a mammary-specific promoter. Applicants also direct the Examiner's attention to the fact that the United States Patent and Trademark Office has granted numerous patents that encompass the production of cloned transgenic ungulates, for example, U.S. Patent No.

5,945,577 issued to Stice et al. and assigned to the University of Massachusetts. Thus, the Patent Office has acquiesced that transgenic ungulates, for example bovines, have an accepted usage in agriculture and for recombinant protein production.

The Examiner also goes on to cite several publications which are described as being "state of the art." Applicants respectfully disagree with this characterization for the following reasons.

Kappell et al. (1992): The examiner alleges that Kappel et al. reports that the individual gene of interest, promoter, enhancer, coding or non-coding sequences present in a transgene construct are important factors that govern the expression of a transgene and that it is unpredictable for generating transgenic animals. Applicants maintain that Kappel et al. represents the state of the art in 1992 for creating transgenic animals where a foreign gene is expressed in an animal. Kappel et al. discuss the fact that as of 1992, the expression of a transgene was often complicated by such factors as the cite of integration of the construct into non-transcribed regions of chromatin. Applicants maintain that the problems associated with the expression of a transgene in a transgenic animal do not apply to the targeted deletion or disruption of a gene in a transgenic animal. The deletion or disruption of a gene will always of necessity prevent the transcription of a gene unlike the possible variability in the expression of an added transgene, and by definition, the targeted deletion or disruption of a gene is not an example of a random integration within the genome. Therefore, Applicants maintain that this is not a relevant nor valid reference by which to judge the current application.

Wu et al. (1997): Applicants maintain that while the Wu et al. Reference describes the difficulties associated generating targeted homozygous deletions in mice using ES cell technology, nevertheless it was widely used in academic research and biotechnology to generate homozygous deletions. Such companies as Lexicon Genetics claim to have used this approach to knock out a large percentage of the genes in the mouse genome, and offer homozygous deletions as one of its primary products. And a full reading of Wu et al demonstrates that even as of 1997 the authors were disclosing methods that remedy the described difficulties: "Certainly, this approach is time-consuming and costly to obtain homozygous or double-knockout mice. Another major concern with the previous gene knock-out strategy is the potentially lethal effect

of the targeted gene. In some cases, gene knockout results in early death of the embryos and young animals, or morphologically and functionally abnormal offspring such as blind and/or handicapped animals. These two limitations of the previous method greatly restrict the application of gene knockout techniques. As a matter of fact, many grant proposals for the targeting of some crucial genes seldom get approved due to potentially lethal concerns. To overcome the above limitations, we have developed a novel strategy by which gene double-knockout can be achieved at the ES cell level instead of waiting for the F2 generation. An even more powerful argument is that, in order to address the lethal concerns, the homozygously targeted gene can be kept silent until it is activated." (Wu et al, 1997 p 340, emphasis by the Applicants).

Furthermore, the Applicants maintain that the Wu et al. Reference published in 1997 does not represent the state of the art as of the filing date of the current application. The focus of the Wu et al. article involves applications in mice ES cells as a vehicle to transport genetic modifications into the germ-line. Applicants maintain that if one skilled in the art were to study Wu et al., they would not determine this to be state of the art because genetically modifying mice through ES cells does not necessarily represent the state of the art in producing transgenic ungulate animals through. Nuclear transfer cloning has been demonstrated to result in successful homozygous targeted deletions in ungulates (Phelps et al., 2003, Science 299(5605): 411-414). Examiner further alleges that Wu et al. suggest that another major concern is the potential lethality of the targeted deletion, concluding that in some cases where genes are deleted in mice through ES cell technology, homozygous knock-out results in early death of embryos and young animals or functionally abnormal offspring. Applicants respectfully direct the examiner to the specification for example at page 4 lines 18-25 that describes that the disruption of the gene in mice did not lead to a lethal phenotype. Unlike Wu et al., the specification does not describe the random homozygous deletion of genes to determine a phenotype, many of which genes may be requisite for normal development. Instead, the specification describes the targeted deletion of a gene demonstrated in another mammal not to be essential for viability, but which when disrupted confers a resistance to a disease state. Applicants respectfully direct the attention of the Examiner to the specification for example at page 42, lines 7-14 that describes the proficiency of the applicants at producing transgenic animals by cloning at a reasonably high efficiency rate.

Applicants cite numerous examples throughout the specification that their superior methodology leads to the successful production of transgenic animals.

Sigmund et al. (2000): The Examiner also cites Sigmund et al. as reporting that the variation in the genetic background contributes to unpredictable resulting phenotypes of transgenic or gene targeted animals. The Examiner also cites Sigmund et al. as reporting that the variation in the genetic background contributes to unpredictable resulting phenotypes of transgenic or gene targeted animals due to the influence of other genes not related per se to the ones being targeted playing a significant role in the resulting phenotype. Applicants maintain that this is indeed the case for many genes in mammals that display a redundancy of function with other genes. However, this application relates to a gene whose gene product itself is the cause of prion disease. The Applicants respectfully submit that such redundancy of function would not reasonably be relevant to the unique case where a specific gene product is the causative agent in a disease as in the case of prion disease.

Nishi et al. (1997): The Examiner cites Nishi et al. as reporting that the nociceptin system plays a role in the modulation of nociceptive threshold and locomotor activity and gives an example that a transgenic mouse lacking the nociceptin receptor does not result in significant differences in nociceptive threshold and locomotor activity as compared to control mice. Again, Applicants maintain that this does not represent state of the art for the following reasons. First of all as Nishi et al. describe in their publication at page 1858, column 2, "the physiological roles of the nociceptin system have not been elucidated yet at the whole animal level." Thus, with no known function of the nociceptin system, the use of a knockout mouse that doesn't correlate to any function is inconsistent with the current application in which transgenic ungulates are raised bearing or lacking the PRP gene and the PRP gene is known to be essential for prion disease. Applicants maintain that it would have been unpredictable for Nishi et al. to describe the phenotype of such a knockout mouse because the role of nociceptin was unknown at the time. In the current invention however, it is known that deletion of the prion-related gene will lead to an animal that is less susceptible to a prion-related disease because there is less expression of the protein precursor that is known to directly cause the disease. Thus, applicants maintain that Nishi et al. is not a relevant description of the state of the art for the current application.

Thus, Applicants maintain that it would not have required undue experimentation for one skilled in the art at the time of the invention to practice the full scope of the invention as claimed. Thus, Applicants respectfully request withdrawal of this rejection.

Rejection Under 35 U.S.C. § 103(a)

The Examiner has rejected claims 1-6, 8, 9 and 23-27 under 35 U.S.C. § 103(a) as being unpatentable over Weissmann et al. (U.S. Patent No. 5,698,763) in view of Wu et al. (1997) and Shani et al. (1992). Applicants respectfully traverse this rejection. The Examiner alleges that Weissmann et al. teach that using DNA targeting molecules that specifically disrupt PRP genes by homologous recombination in transfected animal cells and culturing the transfected animal cells in producing transgenic animals having the deleted PRP gene in the transgenic progeny of said mammals. The Examiner also alleges that Weissmann et al. teach using neomycin or hygromycin selectable marker gene under the control of various promoters in a DNA vector for the selection of the transfected cells. The Examiner alleges that Weissmann et al. report that complete prion genes have been cloned and sequenced in many mammals and that Weissmann et al. allegedly teach making transgenic mammals lacking PRP genes and thus the void of prion proteins. The Examiner also states that Weissmann et al. teach the production of a transgenic mouse having said deletion. However, the Examiner acknowledges that Weissmann et al. do not teach using a heterologous gene under the control of a mammary specific promoter extraneous to the prion gene locus in the production of recombinant protein in the milk of a transgenic ungulate.

The Examiner states that Wu et al. teach a method of making a transgenic knockout animal(***mouse***) by using DNA targeting vectors comprising a marker such as neomycin.

The Examiner states that Shani et al. teach generating transgenic (***mice***) expressing sheep beta-lactoglobulin or human cerumalbumin under the control of the sheep lactoglobulin promoter sequence and it demonstrates that high levels of serum albumin can be expressed in the milk of transgenic (***mice***).

The Examiner alleges that it would have been obvious for one of ordinary skill in the art at the time of the invention to include the heterologous gene as taught by Shani et al. in the DNA targeting vector as taught by Wiessmann et al. and Wu et al. for the production of recombinant

protein in milk because Wu et al. teach using for example neomycin a selection marker gene and Shani et al. teach using transgenic livestock to produce recombinant protein in milk and that it was known in the art to express a heterologous gene and a transgenic animal for the production of its gene product.

Applicants maintain that one skilled in the art would not have been able to combine the teachings of Weissmann et al., Wu et al., and Shani et al. to produce a transgenic ungulate because these three references describe the making of transgenic mice lacking PRP genes (Weissmann et al.), strategies in gene knockout in mice (Wu et al.), and the expression of human serum albumin in the milk of transgenic animals. Applicants believe that the Examiner has attempted to establish that the elements of the invention, albeit in mice, were known, however, establishing that all elements of a combination are known does not per se establish obviousness. Smith Industries Medical Systems, Inc. v. Vital Signs, Inc., 183F.3d 1347, 1356, 51 USPQ2d 1415, 1420-21 (Fed. Cir. 1999). Applicants respectfully note that each of the references discussed here is specific to mice and again call the Examiner's attention to page 17 line 23 to page 18 line 2 of the specification which addresses the differences of gene targeting between mice and cattle and the construction of a genomic library to facilitate the gene targeting in cattle. Furthermore, the Examiner asserts that the claims do not specify the phenotype of the transgenic ungulate and that one skilled in the art would be able to make the claimed transgenic ungulates regardless of the resulting phenotypes with a reasonable expectation of success. Applicants respectfully assert that the claims as now amended specify the phenotype of the transgenic ungulate as being one in which the ungulate is rendered less susceptible for a prion-associated disease. For the foregoing reason, Applicants respectfully traverse the rejection of these claims under 35 U.S.C. § 103(a).

Applicants respectfully submit that the foregoing Amendment place this application in condition for allowance of all pending claims.

No further fees are believed due; however the commissioner is authorized to charge any fee due or refund any credit to Deposit Account No. 13-2725. If the Examiner believes that there are any issues that can be resolved by a telephone conference, or that there are any informalities that can be corrected by an Examiner's amendment, please call the undersigned at 508.756.1212x133.

The Applicants respectfully request entry of the amendments and the reconsideration of the claims. Claims 1 and 22 have been amended. No new matter has been added through the amendments. Claims 1-6, 8, 9 and 22-27 are pending. The Applicants respectfully request reconsideration and withdrawal of the pending rejections under 35 U.S.C. §112, first paragraph, and 35 U.S.C. §103.

Respectfully submitted,

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